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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,521	08/27/2001	Jianyun Dong	22488-710	7109

21971 7590 02/03/2006

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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 02/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/600,521	DONG ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2005 and 17 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47,58,59,61,67-69,71-73 and 115-119* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47, 58, 59, 61, 67-69, 71-73 and 115-119* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 25 August 2005 has been entered.

Claims 47, 58, 59, 61, 67-69, 71-73 and 115-119 are pending in this application.

Applicant's arguments have been fully considered but are not deemed persuasive. The rejections of record are set forth under 35 U.S.C. §112, first paragraph. More particularly, the rejections consist of a rejection of claims 118 and 119 under 35 U.S.C. §112 (Deposit Requirement) and a rejection of all the claims as lacking enablement for *in vivo* use.

35 USC §112 - Deposit Requirement

With respect to the Deposit Requirement, Applicant asserts that the instant specification teaches the sequences for the structural elements that are to be mobilized into intermediate vectors whose sequence maps are readily available. Thus, Applicant asserts one of skill will be able to construct the specific vectors of claims 118 and 119. (e.g., Remarks, p. 8, ¶¶ 1-2). In sum, Applicant asserts that since the maps of the intermediate vectors are available and the specification teaches the sequence of FasL placed downstream of the GFP sequence, then claims 118 and 119 are enabled.

It is respectfully pointed out that each claim is directed to a specific vector, which is necessarily defined by a specific sequence of nuclei acids. That the maps of intermediate vectors are available is of little moment, because even a single nucleotide change (e.g., utilizing different restriction sites within the cloning site of an intermediate vector) would distinguish vectors that otherwise have the requisite structural elements (e.g., tet-responsive element, GFP, FasL).

Put another way, by claiming a specific vector, each claim is defined by a specific sequence for said vector. Therefore, a single unique sequence would correspond to the claimed vector in each of claims 118 and 119. As such, one of skill in the art cannot construct a specific vector without knowledge of the specific sequence for said vector (e.g., variance in cloning sites). The rejection is maintained.

35 USC §112 - Enablement In Vivo

With respect to rejections based on a lack of enablement for practicing the invention *in vivo*, Applicant's assertions are summarized as follows: (1) the apoptotic effect induced via FasL expression will be localized to the tumor and not affect normal cells (Remarks, p. 10, paragraph 1, last sentence); (2) some of the cited art does not support the grounds of rejection (Remarks, p. 10, paragraph 2, first sentence; p. 11, second full paragraph); (3) systemic administration of adenoviral vectors comprising tissue specific and inducible promoters will limit expression of FasL to a particular locus, i.e. tumor cells (Remarks, p. 12, paragraph 1), and is demonstrated to be nonlethal; and (4) direct injection of the adenovirus vector into solid tumors in mice demonstrates therapeutic potential and no lethal effects (Remarks, p. 13, second full paragraph).

At the outset, it should be noted that as written, the claims read on systemic administration of adenoviral vectors to induce cell death in Fas^+ cells. In other words, the claims are not exclusively delimited to direction injection of the vectors into a tumor mass. For example, independent claim 47 is broadly directed to "transducing an adenoviral vector ...into cancer cells".

Thus, the vector can be administered through any route. Similarly, claim 61 is directed to "direction injection of the adenoviral vector among cancer cells". Thus, injection by any route into a patient within whom cancer cells are present meets this claimed limitation.

Applicants first assertion is that the specification teaches a method of treating a tumor by introducing a vector expressing FasL into a second tumor cell, whereby the expressed FasL then interacts with a second tumor cell that is Fas^+ thus inducing apoptosis in said second tumor cell (i.e., bystander effect). None of the claims are so delimited. However, irrespective of what cancer cells are transduced, the unpredictability is borne from systemic administration *and* immunotoxicity of utilizing adenoviral vectors in gene therapy. (e.g., Final Action, mailed 05/17/2005, p. 7, ¶¶ 2-3). Therefore, at least within the context of systemic delivery adenoviral vectors, the immunotoxicity is exclusive from the therapeutic being expressed.

As noted in the Final Action, there is unpredictability with respect to practicing the invention *in vivo* with respect to vector neutralization via anti-adenoviral antibodies, and immunogenicity affecting transgene expression levels and viral vector distribution within the subject. (Final Action, p. 7, citing Green et al. Canc. Gene Therapy, 2002; 9: 1036-42). For example, the duration of transgene expression can be reduced by the host's anti-virus immune

response. Thus, Applicant's assertion that a tissue-specific and an inducible promoter[1] will limit expression to specific target cells is of little moment, where the relevant art suggest that it is unpredictable whether the vector will be delivered to the target in the first place. (Supra, Green, 2002).

Applicant also presents a reference demonstrating that systemic delivery in immunocompetent mice (BALB/c mice) demonstrates that the vector is safe, does not address the unpredictability with respect to vector-neutralization/biodistribution, which would preclude delivery and expression of the transgene in target cells. First, the evidence is comprised in a post-filing publication. (Applicant's effective priority date is 11/06/1998). Second, results in mice are not necessarily extendable to other mammals (e.g., humans, where the virus may rapidly localize in the liver).

In addition, Applicant provides a Declaration by Dr. James S. Norris, which demonstrates that nude mice are injected with cancer cells resulting in tumors forming in the animals' flanks with subsequent injection into different sites of the tumor of the adenoviral vectors expressing FasL. The FasL expression results in significant regression of the growing tumors. The accuracy or significance of the result is not disputed. However, the Declaration does not provide any additional evidence that is not already present in the instant disclosure.

Applicant's second argument is that the cited references Arai et al. or O'Connell et al. do not suggest unpredictability. It is noted that there are references that do support unpredictability, which have not been addressed in Applicant's arguments. (e.g., supra, Green, 2002; Rossi et al.

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[1] It should noted that the broadest claims are not directed to a tissue specific promoter, where independent claim 47 recites the conjunctive "or" before the limitation "an inducible promoter".

J. Hematology, 2003; 88: 212-18). With respect to Arai et al., Applicant's argument is persuasive insofar as the inflammation observed at the site of direct injection into tumor mass does not result in toxic effects.

In addition, with respect to O'Connell et al., Applicant asserts that in the mouse model studied, no immune cell death or induction of an inflammatory response is observed as a result of FasL interacting with normal cells that are Fas^+.

Further, Applicant asserts that utilizing tissue specific promoters limits expression to target cells only. Applicant's arguments are not found persuasive, because adenovirus can localize to non-target tissue owing to the characteristics of the vector and the host (e.g., localization in liver). Further, the claims are not limited to tissue specific promoters (e.g., independent claim 47), but encompass any inducible promoter. Thus any amount of expression (e.g., leaky expression) will result in FasL expression (e.g., vectors localized in non-target tissue).

With respect to the unintended effects of immune cell death and induction of an inflammatory response (immunotoxicity), Applicant is correct in stating that the specification does not teach that expression of FasL leads to unintended effects of immune cell death or induction of an inflammatory response (e.g., FasL interaction with non-target or normal Fas^+ cells). However, Applicant's examples are limited to expression of FasL in nude mice (immunocompromised). In addition, results in mice would not necessarily translate to predictability for practicing the invention in larger mammals (e.g., human subjects). In any event, O'Connell teaches that there is a reasonable level of unpredictability in expressing a FasL

in vivo insofar as any Fas^+ cell will interact with the ligand, whereby adverse effects include immune cell death or immunotoxicity.

Applicant's third argument is that systemic administration of a vector with a tissue specific and inducible promoter is demonstrated to be therapeutic and nonlethal. This argument has been addressed in the discussion above of Applicant's first argument. In sum, based on the host (e.g., human) there is unpredictability with systemic administration, as to whether the vector is actually delivered to the desired target cells/tissue.

Thus, regulation of expression would not be determinative with respect to the level of unpredictability. Further, it should be noted, that the claims are not exclusively directed to the adenovector comprising a tissue-specific and inducible promoter (e.g., claim 47).

Applicant's last argument has also been addressed in view of the interpretations of the claims stated above. Applicant asserts that direction injection into the tumor mass demonstrates therapeutic potential and non-lethality. However, as written, the claims are not directed exclusively to direct injection into the tumor mass. Furthermore, results in mice are not necessarily predictive of results that would be observed in immunocompetent and/or larger mammals.

In sum, neither the amendment nor Applicant's arguments are deemed sufficient to obviate the grounds of rejection of record and discussed in the foregoing. The rejections are maintained.

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636

DANIEL M. SULLIVAN
PATENT EXAMINER